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ORIGINAL REPORT

Breast Cancer Family History and Contralateral Breast Cancer Risk in Young Women: An Update From the Women's Environmental Cancer and Radiation Epidemiology Study

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ABSTRACT

Purpose

The Women's Environmental Cancer and Radiation Epidemiology (WECARE) study demonstrated the importance of breast cancer family history on contralateral breast cancer (CBC) risk, even for noncarriers of deleterious *BRCA1/2* mutations. With the completion of WECARE II, updated risk estimates are reported. Additional analyses that exclude women negative for deleterious mutations in *ATM*, *CHEK2**1100delC, and *PALB2* were performed.

Patients and Methods

The WECARE Study is a population-based case-control study that compared 1,521 CBC cases with 2,212 individually matched unilateral breast cancer (UBC) controls. Participants were younger than age 55 years when diagnosed with a first invasive breast cancer between 1985 and 2008. Women were interviewed about breast cancer risk factors, including family history. A subset of women was screened for deleterious mutations in *BRCA1/2*, *ATM*, *CHEK2**1100delC, and *PALB2*. Rate ratios (RRs) were estimated using multivariable conditional logistic regression. Cumulative absolute risks (ARs) were estimated by combining RRs from the WECARE Study and population-based SEER*Stat cancer incidence data.

Results

Women with any first-degree relative with breast cancer had a 10-year AR of 8.1% for CBC (95% CI, 6.7% to 9.8%). Risks also were increased if the relative was diagnosed at an age younger than 40 years (10-year AR, 13.5%; 95% CI, 8.8% to 20.8%) or with CBC (10-year AR, 14.1%; 95% CI, 9.5% to 20.7%). These risks are comparable with those seen in *BRCA1/2* deleterious mutation carriers (10-year AR, 18.4%; 95% CI, 16.0% to 21.3%). In the subset of women who tested negative for deleterious mutations in *BRCA1/2*, *ATM*, *CHEK2**1100delC, and *PALB2*, estimates were unchanged. Adjustment for known breast cancer single-nucleotide polymorphisms did not affect estimates.

Conclusion

Breast cancer family history confers a high CBC risk, even after excluding women with deleterious mutations. Clinicians are urged to use detailed family histories to guide treatment and future screening decisions for young women with breast cancer.

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INTRODUCTION

A family history of breast cancer is a strong and consistent risk factor for breast cancer. Compared with women without a family history, those with a positive family history have a two- to four-fold increased risk of developing breast cancer, which depends on the number of affected relatives and their ages at diagnosis.[1,2] Among breast cancer survivors, second primary breast cancer incidence rates exceed those of a first breast cancer in the general population,[3,4] and risk of contralateral breast cancer (CBC) is increased further for women with a breast cancer family history.[5-9]

Deleterious mutations in the *BRCA1* and *BRCA2* genes, although relatively rare, have been associated with increased risks of breast cancer, as

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have mutations in DNA damage response genes *PALB2*, *CHEK2*, and *ATM*.[10-15] Recent collaborative genotyping efforts identified over 100 commonly occurring single-nucleotide polymorphisms (SNPs) that are associated with small increases in risk of first primary breast cancer.[16-49]

The Women's Environmental Cancer and Radiation Epidemiology (WECARE) Study is a population-based, case-control study of CBC cases and matched controls with unilateral breast cancer (UBC). In the first phase of the WECARE Study wherein analyses involved a considerably smaller sample than that of the current study, we reported that family history remained a strong risk factor for CBC in the absence of *BRCA1/2* mutations.[50,51] Among noncarriers of *BRCA1/2* mutations, any history of breast cancer in first-degree relatives (mother, sisters, or daughters) versus no such history was associated with a nearly two-fold increased CBC risk. Additional increases in risk were associated with family history of relatives diagnosed at a young age and relatives with bilateral disease. We also have reported an increased CBC risk associated with a polygenic risk score (PRS) that comprises 67 common breast cancer susceptibility SNPs (per-risk allele trend rate ratio [RR], 1.04; 95% CI, 1.03 to 1.06).[52]

The completion of the second phase of WECARE allows us to clarify the relationship between family history of breast cancer and CBC risk. We report on a larger, updated study of 3,733 women as well as a subset of women who tested negative for deleterious mutations in *BRCA1*, *BRCA2*, *ATM*, *CHEK2**1100delC, and *PALB2*. Furthermore, we adjusted for known common breast cancer susceptibility SNPs by incorporating a PRS.

PATIENTS AND METHODS

The WECARE Study Population

The WECARE Study is a multicenter, population-based, case-control study of CBC cases and individually matched UBC controls conducted in two phases: the WECARE I Study[53] and the WECARE II Study.[54] Eligible women were identified through eight population-based cancer registries: six in the United States and one each in Canada and Denmark (Table 1). The study protocol was approved by institutional review boards at each site and by the ethics committee system in Denmark.

Cases were women diagnosed between 1985 and 2008 with a first invasive breast cancer that had not spread beyond regional lymph nodes at diagnosis and had a second primary CBC diagnosed at least 1 year after the first diagnosis (1 year for the WECARE I Study; 2 years for the WECARE II Study), younger than 55 years at first diagnosis, without previous or intervening cancer diagnoses except nonmelanoma skin cancer or cervical carcinoma in situ, alive at contact, willing to provide informed consent and a blood or saliva sample, and residents of the same cancer registry reporting region for both diagnoses. These eligibility criteria, in addition to no contralateral mastectomy, were used to select controls individually matched to cases (2:1 in the WECARE I Study; 1:1 in the WECARE II Study) on the basis of the following criteria: diagnosis age (5-year strata), diagnosis year (4-year strata), cancer registry region, and ethnicity. The WECARE I Study cases and controls also were countermatched on cancer registry–reported treatment with radiation such that two members of the case-control triad had received radiation therapy for their index breast cancer to improve statistical power to detect gene-radiation interactions. The at-risk period for each control was the same length as the interval between the first and second cancer diagnoses of her matched case. This at-risk period began on the control's date of diagnosis and ended on the reference date defined by the end of her at-risk period.

Participants were interviewed by telephone using a structured questionnaire to obtain data on known or suspected breast cancer risk factors, including demographics, medical and reproductive history, hormone use, smoking, and alcohol intake. Detailed breast cancer family history was obtained and included the relative's age at diagnosis and whether the disease was bilateral. Participants who reported having a mother, sister, or daughter with breast cancer were classified as having first-degree family history; women with at least one grandmother, aunt, or half-sister with breast cancer were classified as having second-degree family history. When considering a relative's age at diagnosis, we used the youngest age reported for analyses. Thirty-eight participants (13 cases, 25 controls) were adopted or had unknown family history; they were included in models with an indicator variable.[60]

Data on treatment and tumor characteristics, including estrogen receptor and progesterone receptor status, were obtained from cancer registry records or by abstracting medical records (eg, pathology, surgery, systemic adjuvant reports) and radiation oncology clinic notes. For participants with missing treatment information in their medical records (chemotherapy, 4%; hormonal therapy, 5%), self-reported data were used.

Genotyping

The WECARE Study participants were genotyped for known breast cancer susceptibility SNPs to create a PRS. Briefly, blood samples from the WECARE I Study participants were genotyped with the HumanOmni1-Quad BeadChip (Illumina, San Diego, CA). Default Omni1-Quad cluster definitions from Illumina were used to call genotypes. Saliva samples from the WECARE II Study participants were genotyped using two custom Infinium iSelect arrays (Illumina). IMPUTE2 software was used to impute missing genotypes on the basis of the cosmopolitan panel of reference haplotypes from the 1000 Genomes Project (phase 1, March 2012 release).[61] Thirty-five SNPs had imputed missing genotypes. Imputation quality and accuracy filters, as well as the individual 67 breast cancer susceptibility SNPs and their relation to CBC risk, have been previously described.[52] Population substructure was investigated using EIGENSTRAT, which generated principal components (eigenvectors) included in analyses.[62] In addition, 705 cases and 1,398 controls in the WECARE I Study were screened for *BRCA1/2* mutations,[55] 708 cases and 1,397 controls for *ATM*,[56,57] 708 cases and 1,395 controls for *CHEK2**1100delC,[58] and 559 cases and 565 controls for *PALB2*.[59]

Statistical Analyses

In the WECARE Study design, controls are independently sampled from the failure time risk sets; thus, the estimated parameters are RRs in the proportional hazards model for cohort data.[63,64] Multivariable-adjusted RRs and corresponding 95% CIs were estimated by fitting conditional logistic regression models. To account for the countermatched design in the WECARE I Study, models included log-weight offset terms. Models included the following known and suspected CBC risk factors: age at first breast cancer diagnosis, age at menarche, parity, age at menopause if occurred at least 2 years before the first diagnosis, histology of first diagnosis, stage of first diagnosis, and chemotherapy/hormonal treatment of first diagnosis. The age cut point of 40 years was chosen to take advantage of our sample size in a younger population. To include all women, missing information on a covariate was represented by an indicator variable.[60] We also conducted analyses in the subset of the WECARE Study participants screened for mutations in *BRCA1*, *BRCA2*, *ATM*, *CHEK**1100delC, and *PALB2*, excluding carriers.

We created an unweighted PRS that comprised 67 SNPs previously shown to be associated with increased breast cancer risk.[16] For each study participant, genotypes were determined at each of the 67 loci. An unweighted risk score was calculated as the integer count of risk alleles at each directly genotyped locus or for imputed loci, the imputed dosage (values between 0 and 2, inclusive). If the published[16] minor allele odds ratio was < 1, the major allele was considered the risk allele for the PRS. Conversely, if the published[16] minor allele odds ratio was > 1, the minor

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Table 1. Characteristics of the WECARE Study, United States and Denmark, 1985 to 2008

Variable	CBC Cases, No. (%)	UBC Controls, No. (%)
No. of participants	1,521	2,212
Median age at first diagnosis, years (range)	46 (24-54)	46 (23-54)
Median age at reference date, years (range)	53 (27-73)	52 (27-71)
Median length of at-risk period, years[a] (range)	6.3 (1.0-19.8)	5.5 (1.0-19.8)
Median PRS for all ethnicities (range)	63.2 (43.5-78.7)	62.0 (43.5-82.5)
Study area		
California[b]	658 (43)	967 (44)
Canada[c]	159 (10)	157 (7)
Denmark[d]	279 (18)	457 (21)
Iowa[e]	201 (13)	314 (14)
Seattle[f]	224 (15)	317 (14)
Year of first diagnosis		
1985-1988	238 (16)	467 (21)
1989-1992	415 (27)	647 (29)
1993-1996	427 (28)	632 (29)
1997-2008	441 (29)	466 (21)
Ethnicity		
Non-Hispanic white	1,335 (88)	1,978 (89)
Hispanic white	69 (5)	93 (4)
Black	55 (4)	76 (3)
Asian or other	62 (4)	65 (3)
Age at menarche, years		
Never had a period	3 (0)	6 (0)
< 13 (range, 8-12)	724 (48)	965 (44)
≥ 13 (range, 13-19)	791 (52)	1,239 (56)
Unknown	3 (0)	2 (0)
No. of full-term pregnancies		
0	322 (21)	412 (19)
1	271 (18)	341 (15)
2	559 (37)	842 (38)
3	256 (17)	387 (18)
≥ 4 (range, 4-14)	108 (7)	225 (10)
Unknown	5 (0)	5 (0)
Menopausal status/age at menopause (2 years before first diagnosis)		
Premenopausal	1,124 (74)	1,676 (76)
Postmenopausal < 45 years	195 (13)	282 (13)
Postmenopausal ≥ 45 years	194 (13)	240 (11)
Unknown	8 (1)	14 (1)
Histology of first diagnosis		
Ductal	1,205 (79)	1,772 (80)
Lobular	179 (12)	223 (10)
Medullary	51 (3)	65 (3)
Tubular/mucinous	42 (3)	80 (4)
Other	40 (3)	68 (3)
Unknown	4 (0)	4 (0)
Stage of first diagnosis		
Local	1,061 (70)	1,442 (65)
Regional	448 (29)	759 (34)
Unknown	12 (1)	11 (1)
ER status of first diagnosis[g]		
Positive	797 (52)	1,254 (57)
Negative	467 (31)	561 (25)
Other/unknown[g]	257 (17)	397 (18)
PR status of first diagnosis[g]		
Positive	687 (45)	1,083 (49)
Negative	442 (29)	549 (25)
Other/unknown[g]	392 (26)	580 (26)
Chemotherapy for first diagnosis		
No	699 (46)	923 (42)
Yes	822 (54)	1,289 (58)
Radiation treatment of first diagnosis		
No	641 (42)	522 (24)
Yes	880 (58)	1,689 (76)
Unknown	0 (0)	1 (0)
Hormone treatment of first diagnosis		
No	964 (63)	1,270 (57)
Yes	557 (37)	940 (43)
Unknown	0 (0)	2 (0)
WECARE Study phase		
I	708 (47)	1,399 (63)
II	813 (53)	813 (37)
WECARE I participants		
Any *BRCA1* or *BRCA2* deleterious mutation, *ATM* truncating mutation, *CHEK2**1100delC, or *PALB2* truncating mutation[h]		
Yes[i]	130 (18)	93 (7)
No	547 (77)	556 (40)
Unknown if mutations in any of the genes[j]	31 (4)	750 (54)
BRCA1 or *BRCA2* mutations[h]		
BRCA1 or *BRCA2* deleterious mutation[k]	109 (15)	76 (5)
No deleterious *BRCA1* or *BRCA2* mutations	596 (84)	1,322 (95)
Not tested for *BRCA1* or *BRCA2* mutations	3 (0)	1 (0)
ATM truncating mutations[h]		
Yes	12 (2)	8 (1)
No	696 (98)	1,389 (99)
Not tested for *ATM* mutations	0 (0)	2 (0)
*CHEK2**1100delC[h]		
Yes	7 (1)	10 (1)
No	701 (99)	1,385 (99)
Not tested for *CHEK2**1100delC mutations	0 (0)	4 (0)
PALB2 truncating mutations[h]		
Yes	3 (0)	0 (0)
No	556 (79)	565 (40)
Not tested for *PALB2* mutations	149 (21)	834 (60)

(continued in next column)

Abbreviations: CBC, contralateral breast cancer; ER, estrogen receptor; PR, progesterone receptor; PRS, polygenic risk score; UBC, unilateral breast cancer; WECARE, Women's Environmental Cancer and Radiation Epidemiology.

[a]The time between a participant's first breast cancer and her CBC defined her at-risk period. For a matched control, her case's at-risk period was added to the control's date of UBC, and the date on which the at-risk period ended defined her reference date.

[b]Four study centers: Los Angeles County Cancer Surveillance Program, The Cancer Surveillance Program of Orange County/San Diego–Imperial Organization for Cancer Control, Greater Bay Area Cancer Registry (San Francisco Bay Area region and Santa Clara region), and Sacramento and Sierra Center Registry (Sacramento region).

[c]The Ontario Cancer Registry.

[d]The Danish Breast Cancer Cooperative Group Database supplemented by the Danish Cancer Registry.

[e]The State Health Registry of Iowa.

[f]Cancer Surveillance System of the Fred Hutchinson Cancer Research Center.

[g]Refers to receptor status of the first primary breast cancer. The other/unknown category comprises women in whom no laboratory test was performed, the test was performed and the results unknown, or the test performed and the results borderline.

[h]Screening was performed for the WECARE I Study participants, including 705 CBC cases and 1,398 UBC controls screened for mutations in *BRCA1* or *BRCA2*;[55] 708 CBC cases and 1,397 UBC controls genotyped for mutations in *ATM*;[56,57] 708 CBC cases and 1,395 UBC controls genotyped for the *CHEK2**1100delC mutation;[58] and 559 CBC cases and 565 UBC controls genotyped for mutations in *PALB2*.[59]

[i]One CBC case had deleterious mutations in both *BRCA* and *CHEK2**1100delC. One UBC control had deleterious mutations in both *BRCA* and *ATM*.

[j]The participants in this category were genotyped and known to have no deleterious mutations in some of the genes but not all, so they are categorized as unknown.

[k]Three CBC cases and two UBC controls had at least one *BRCA1* or *BRCA2* deleterious mutation but had unknown PRS information.

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allele was considered the risk allele for the PRS. A PRS trend variable was constructed using the median value of each PRS quartile in the WECARE Study population[52]; the trend variable was included as a covariate in the subset analyses to adjust multivariable models further.

Cumulative 10-year absolute risks (ARs) of CBC according to breast cancer family history status were estimated using a previously described methodology.[50,55] Briefly, prevalences and RRs were estimated directly from WECARE Study data and combined with population-based SEER*Stat software cancer incidence data for women ages 18 to 54 years diagnosed between 1985 and 2008 for comparability with women in the WECARE Study.[65] All analyses were performed in SAS 9.4 statistical software (SAS Institute, Cary, NC).

RESULTS

Characteristics of the 1,521 cases and 2,212 controls included in analyses are listed in Table 1. The median age at first diagnosis was 46 years. The majority of participants were non-Hispanic white and had localized estrogen receptor– and progesterone receptor–positive first breast cancers. Among participants tested for *BRCA1*, *BRCA2*, *ATM*, *CHEK2**1100delC, or *PALB2* mutations, 130 cases (18%) and 93 controls (7%) had at least one deleterious mutation.

CBC risk of participants with a first-degree family history of breast cancer was nearly twice that for those without a family history (RR, 1.9; 95% CI, 1.6 to 2.3; Table 2). CBC risk for participants with only a second-degree family history was 40% higher than that of those without a family history (RR, 1.4; 95% CI, 1.2 to 1.7). CBC risk was highest for participants who had a first-degree relative with bilateral disease (RR, 3.4; 95% CI, 2.4 to 5.0).

The association between family history and CBC risk differed by diagnosis age of the affected relative (Table 2). When the first-degree relative was younger than 40 years at diagnosis, CBC risk was more than three-fold higher (RR, 3.3; 95% CI, 2.2 to 5.1) compared with participants with no breast cancer family history. Among those with a first-degree relative diagnosed with bilateral breast cancer younger than 40 years, CBC risk was > 10-fold higher (RR, 10.3; 95% CI, 4.2 to 25.7). Results were similar, although attenuated, when the age cut point of 45 years was used (results not shown).

In analyses restricted to a subset of WECARE Study participants screened for and known to not carry any deleterious mutations in *BRCA1*, *BRCA2*, *ATM*, *CHEK2**1100delC, or *PALB2*, CBC risk associated with having any affected first- or second-degree relative remained elevated (RR, 1.8; 95% CI, 1.3 to 2.4) and did not change after adjusting for PRS (Table 3). Furthermore, the

Table 2. Association Between Family History of Breast Cancer and Risk of CBC in the WECARE Study, United States and Denmark, 1985 to 2008

Family History of Breast Cancer*	CBC Cases No. (%)	UBC Controls No. (%)	RR (95% CI)†
No first- or second-degree relative with breast cancer‡	666 (44)	1,239 (57)	1.0
Any first- or second-degree relative with breast cancer	842 (55)	948 (43)	1.7 (1.5 to 2.0)
Any first-degree relative with breast cancer	498 (33)	470 (21)	1.9 (1.6 to 2.3)
Any second-degree relative with breast cancer	551 (37)	655 (30)	1.6 (1.3 to 1.9)
No first-degree relative with breast cancer, second-degree relative with breast cancer	344 (23)	478 (22)	1.4 (1.2 to 1.7)
No. of first-degree relatives with breast cancer			
No first- or second-degree relative with breast cancer	666 (44)	1,239 (57)	1.0
1	414 (27)	401 (18)	1.9 (1.6 to 2.3)
≥ 2	84 (6)	69 (3)	2.1 (1.5 to 3.0)
Age at diagnosis (years) of WECARE Study participant and first-degree relative with breast cancer§			
No first- or second-degree relative with breast cancer	666 (44)	1,239 (57)	1.0
WECARE Study participant < 40	101 (6)	101 (5)	2.0 (1.3 to 3.0)
WECARE Study participant ≥ 40	397 (26)	369 (17)	1.9 (1.6 to 2.3)
Relative with breast cancer < 40‖	72 (5)	48 (2)	3.3 (2.2 to 5.1)
Relative with breast cancer ≥ 40‖	410 (27)	410 (19)	1.8 (1.5 to 2.1)
WECARE Study participant < 40, relative with breast cancer < 40‖	28 (2)	18 (1)	3.1 (1.5 to 6.4)
WECARE Study participant < 40, relative with breast cancer ≥ 40‖	69 (4)	81 (4)	1.5 (1.0 to 2.3)
WECARE Study participant ≥ 40, relative with breast cancer < 40‖	44 (3)	30 (1)	3.4 (2.0 to 5.7)
WECARE Study participant ≥ 40, relative with breast cancer ≥ 40‖	341 (23)	329 (15)	1.8 (1.5 to 2.2)
Age (years) and bilaterality of first-degree relatives with breast cancer§			
No first- or second-degree relative with breast cancer	666 (44)	1,239 (57)	1.0
Unilateral breast cancer only‖	402 (27)	414 (19)	1.7 (1.5 to 2.1)
Bilateral breast cancer‖	96 (6)	56 (3)	3.4 (2.4 to 5.0)
< 40, unilateral breast cancer‖	44 (3)	41 (2)	2.2 (1.3 to 3.6)
< 40, bilateral breast cancer‖	28 (2)	7 (0)	10.3 (4.2 to 25.7)
≥ 40, unilateral breast cancer‖	343 (23)	361 (17)	1.7 (1.4 to 2.0)
≥ 40, bilateral breast cancer‖	67 (4)	49 (2)	2.6 (1.7 to 4.0)

Abbreviations: CBC, contralateral breast cancer; RR, rate ratio; UBC, unilateral breast cancer; WECARE, Women's Environmental Cancer and Radiation Epidemiology.
*Thirty-eight women (13 CBC cases and 25 UBC controls) were adopted or had missing information on family history of breast cancer.
†Adjusted for age at first breast cancer diagnosis, age at menarche, number of full-term pregnancies as of first diagnosis, age at menopause 2 years before first diagnosis, chemotherapy or hormonal treatment at first diagnosis, histology of first diagnosis, and stage at first diagnosis. Age at first diagnosis was omitted as a confounder for any analyses where age of the WECARE Study participant was included as part of the main variable of interest.
‡The reference category for all models was no first- or second-degree relative with breast cancer.
§Twenty-eight women were excluded (16 CBC cases and 12 UBC controls) because of missing information on the relative's age at diagnosis.
‖First-degree relative.

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association of bilateral breast cancer family history with CBC risk remained statistically significantly elevated in this subset of participants (RR, 3.7; 95% CI, 1.7 to 8.2), and adjustment for PRS had a negligible effect on risk estimates (RR, 3.4; 95% CI, 1.5 to 7.4).

The cumulative 10-year AR of CBC for participants without a family history of breast cancer was 4.3% (95% CI, 4.1% to 4.5%; Table 4). For participants with a first-degree family history of breast cancer, the 10-year AR of CBC was 8.1% (95% CI, 6.7% to 9.8%). Risk increased further when the first-degree relative was diagnosed with breast cancer at an age younger than 40 years (10-year AR, 13.5%; 95% CI, 8.8% to 20.8%) or if the first-degree relative was diagnosed with bilateral breast cancer (10-year AR, 14.1%; 95% CI, 9.5% to 20.7%). In addition, risk was the highest when the first-degree relative was diagnosed with bilateral breast cancer before age 40 years (10-year AR, 36.3%; 95% CI, 14.5% to 90.5%). The cumulative 10-year ARs of CBC by family history status for noncarriers of deleterious mutations in *BRCA1*, *BRCA2*, *ATM*, *CHEK2**1100delC, or *PALB2* were similar to those for all women (Table 4).

DISCUSSION

With the completion of WECARE II, a study of larger size, we found that a first-degree family history of breast cancer nearly doubled CBC risk, even in a subset of women screened for and

Table 3. Association of Family History of Breast Cancer and Risk of CBC in Screened Participants With No Known Deleterious Mutations in Certain Genes in the WECARE Study, United States and Denmark, 1985 to 2008

	Study Subset Genotyped for Mutations in *BRCA1*, *BRCA2*, *ATM*, *CHEK2**1100delC, and *PALB2*, Excluding Carriers			
Family History of Breast Cancer[a]	Cases, No. (%)	Controls, No. (%)	Not Adjusted for PRS[b] RR (95% CI)	Adjusted for PRS[c] RR (95% CI)
No first- or second-degree relative with breast cancer[d]	249 (46)	325 (60)	1.0	1.0
Any first- or second-degree relative with breast cancer	294 (54)	216 (40)	1.8 (1.3 to 2.4)	1.8 (1.3 to 2.5)
Any first-degree relative with breast cancer	162 (30)	108 (20)	2.0 (1.4 to 3.0)	2.0 (1.4 to 2.9)
Any second-degree relative with breast cancer	200 (37)	151 (28)	1.7 (1.2 to 2.4)	1.7 (1.2 to 2.4)
No first-degree relative with breast cancer, second-degree relative with breast cancer	132 (24)	108 (20)	1.6 (1.1 to 2.3)	1.6 (1.1 to 2.4)
No. of first-degree relatives with breast cancer				
No first- or second-degree relative with breast cancer	249 (46)	325 (60)	1.0	1.0
1	143 (26)	94 (17)	2.1 (1.4 to 3.1)	2.1 (1.4 to 3.2)
≥ 2	19 (4)	14 (3)	1.5 (0.6 to 3.6)	1.3 (0.5 to 3.1)
Age at diagnosis (years) of WECARE Study participant and first-degree relative with breast cancer[e]				
No first- or second-degree relative with breast cancer	249 (46)	325 (60)	1.0	1.0
WECARE Study participant < 40	18 (3)	17 (3)	0.6 (0.2 to 1.6)	0.5 (0.2 to 1.4)
WECARE Study participant ≥ 40	144 (27)	91 (17)	2.4 (1.6 to 3.7)	2.5 (1.6 to 3.7)
Relative with breast cancer < 40[f]	17 (3)	10 (2)	3.7 (1.4 to 9.8)	4.8 (0.9 to 24.8)
Relative with breast cancer ≥ 40[f]	140 (26)	96 (18)	1.8 (1.2 to 2.7)	3.0 (0.9 to 9.8)
WECARE Study participant < 40, relative with breast cancer < 40[f]	4 (1)	2 (0)	1.9 (0.3 to 14.7)	1.6 (0.2 to 12.2)
WECARE Study participant < 40, relative with breast cancer ≥ 40[f]	14 (3)	15 (3)	0.5 (0.2 to 1.5)	0.5 (0.2 to 1.4)
WECARE Study participant ≥ 40, relative with breast cancer < 40[f]	13 (2)	8 (1)	4.1 (1.4 to 12.3)	3.9 (1.3 to 11.4)
WECARE Study participant ≥ 40 years, relative with breast cancer ≥ 40[f]	126 (23)	81 (15)	2.2 (1.5 to 3.4)	2.2 (1.5 to 3.4)
Age and laterality of first-degree relatives with breast cancer[e]				
No first- or second-degree relative with breast cancer	249 (46)	325 (60)	1.0	1.0
UBC only[f]	132 (24)	93 (17)	1.8 (1.2 to 2.7)	1.8 (1.2 to 2.7)
Bilateral breast cancer[f]	30 (6)	15 (3)	3.7 (1.7 to 8.2)	3.4 (1.5 to 7.4)
< 40, UBC[f]	11 (2)	6 (1)	3.7 (1.2 to 12.0)	3.5 (1.1 to 11.1)
< 40, bilateral breast cancer[f]	6 (1)	4 (1)	3.0 (0.5 to 16.9)	2.8 (0.5 to 14.7)
≥ 40, UBC[f]	116 (21)	85 (16)	1.6 (1.0 to 2.4)	1.6 (1.0 to 2.4)
≥ 40, bilateral breast cancer[f]	24 (4)	11 (2)	4.2 (1.7 to 10.4)	3.9 (1.5 to 9.7)

Abbreviations: CBC, contralateral breast cancer; PRS, polygenic risk score; RR, rate ratio; UBC, unilateral breast cancer; WECARE, Women's Environmental Cancer and Radiation Epidemiology.

[a]There are 543 CBC cases and 541 controls reported for the following reasons: Of the 708 CBC cases and 1,399 UBC controls in the WECARE I Study, 781 (31 CBC cases and 750 UBC controls) were excluded because of no information about carrying a *BRCA* deleterious, *ATM* truncating, *CHEK2**1100delC, or *PALB2* truncating mutation. An additional 233 women (130 CBC cases and 103 UBC controls) were excluded because they carried a *BRCA* deleterious, *ATM* truncating, *CHEK2**1100delC, or *PALB2* truncating mutation or were part of a duo or triad which could not contribute to the analyses because a member was a carrier. Ten women (four CBC cases and six UBC controls) were adopted or had missing information on family history of breast cancer, one of whom (UBC control) carried a deleterious mutation.

[b]Adjusted for age at first breast cancer diagnosis, age at menarche, number of full-term pregnancies as of first diagnosis, age at menopause 2 years before first diagnosis, chemotherapy or hormonal treatment at first diagnosis, histology of first diagnosis, and stage at first diagnosis. Age at first diagnosis is omitted as a confounder for analyses where age of the WECARE Study participant was included as part of the main variable of interest.

[c]Adjusted as in ‡ as well as for eigenvectors and PRS trend variable by incorporating 67 common breast cancer susceptibility variants[52] constructed using medians of quartile midpoints in the WECARE Study population. Age at first diagnosis was omitted as a confounder for analyses where age of the WECARE Study participant was included as part of the main variable of interest.

[d]The reference category for all models was no first- or second-degree relative with breast cancer.

[e]Seven participants (five CBC cases and two UBC controls) were excluded because of missing information on relative's age at breast cancer diagnosis.

[f]First-degree relative.

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Table 4. Cumulative Ten-Year Absolute Risk of CBC According to Family History

Family History of Breast Cancer	Ten-Year Cumulative Absolute Risk (%)* of CBC (95% CI)	
	All Women	Noncarriers of Deleterious Mutations in *BRCA1, BRCA2, ATM, CHEK2**1100delC, and *PALB2*
No first- or second-degree family history	4.3 (4.1 to 4.5)	4.2 (3.9 to 4.6)
Any first-degree family history	8.1 (6.7 to 9.8)	8.3 (5.5 to 12.6)
Only second-degree family history	6.0 (4.9 to 7.4)	6.6 (4.4 to 10.0)
First-degree relative with breast cancer < 40 years	13.5 (8.8 to 20.8)	14.5 (5.4 to 38.7)
First-degree relative with breast cancer ≥ 40 years	7.5 (6.1 to 9.1)	7.4 (4.9 to 11.4)
Unilateral breast cancer history only	7.4 (6.1 to 9.0)	7.4 (4.8 to 11.4)
Bilateral breast cancer history	14.1 (9.5 to 20.7)	14.5 (6.4 to 32.5)
First-degree relative with bilateral breast cancer < 40 years	36.3 (14.5 to 90.5)	—

Abbreviations: —, no estimate obtained because of small sample size; CBC, contralateral breast cancer; WECARE, Women's Environmental Cancer and Radiation Epidemiology.
*Risk determined actuarially using previously described methodology[50,55] that combined annual SEER CBC rates and adjusted rate ratios from the WECARE Study.

known to not carry deleterious mutations in *BRCA2*, *BRCA2*, *ATM*, *CHEK2**1100delC, or *PALB2*, and after adjustment for PRS. Given the larger sample size, we were able to investigate the combined effect of bilateral breast cancer and young age (< 40 years) at breast cancer diagnosis in first-degree relatives on CBC risk and report a 10-fold increased risk of developing second primary breast cancer and a 10-year absolute CBC risk of 36%. Of note, having a first-degree relative diagnosed with bilateral breast cancer conferred a 10-year absolute CBC risk of approximately 14%, as did having a first-degree relative diagnosed with breast cancer at a young age (< 40 years), which is comparable to our previously estimated 10-year absolute CBC risk of 18% for *BRCA1/2* deleterious mutation carriers.[55]

Similar associations with family history are well-established for first primary breast cancer. In a meta-analysis of first primary breast cancer, Pharoah et al[2] reported relative risks of 2.1 associated with first-degree family history of breast cancer and 1.5 associated with second-degree family history versus no family history. For women with first-degree relatives diagnosed with breast cancer before age 50 years, breast cancer risk was increased more than three-fold. A pooled analysis of 52 epidemiologic studies reported similar findings,[1] with a nearly two-fold higher breast cancer risk associated with first-degree family history of breast cancer and a nearly three-fold higher risk associated with family history of early-onset breast cancer (age < 35 years). The current findings for CBC risk are consistent with the results from the few studies that reported on the association between breast cancer family history and CBC risk. In a prospective cohort study, Bernstein et al[3] found that women with a first-degree relative with breast cancer had a nearly two-fold greater CBC risk than women with no relatives with breast cancer. Furthermore, among women with a first-degree relative diagnosed with breast cancer at a young age (≤ 45 years), CBC risk was nearly three-fold greater than that of women without a family history. Our findings also confirm earlier reports of increased CBC risk associated with family history of early-onset breast cancer and family history of bilateral breast cancer.[5-9] To our knowledge, the current report is the first of a 10-fold increased CBC risk for women who have relatives with early-onset bilateral disease.

Previous studies have shown that germline mutations in *BRCA1* and *BRCA2* as well as *PALB2, CHEK2,* and *ATM* mutations are associated with risk of first breast cancer.[10-15] Missense mutations in *ATM* have been shown to increase CBC risk in women exposed to radiation therapy, and mutations in *BRCA1*, *BRCA2*, *PALB2*, and *CHEK2* have been shown to be associated with risk of second primary breast cancer.[55,56,59,66,67] Kuchenbaecker et al[68] reported rapid increases in primary breast cancer incidence in young women (until ages 30 to 40 years for *BRCA1* mutation carriers and until ages 40 to 50 years for *BRCA2* mutation carriers) as well as increased primary breast cancer risk for *BRCA1/2* mutation carriers with a first- and second-degree family history of breast cancer. They did not report on the effect of family history on CBC risk. In the subset of WECARE Study participants screened for deleterious mutations in *BRCA1*, *BRCA2*, *ATM*, *CHEK2**1100delC, and *PALB2*, the analyses that excluded mutation carriers found that a first-degree family history of breast cancer remained a statistically significant CBC risk factor. Women having a first-degree family history of bilateral breast cancer had a more than three-fold increased risk of CBC. Furthermore, these associations were negligibly affected by adjustment for PRS of common breast cancer susceptibility SNPs in this subset as well as the entire WECARE Study cohort. These findings highlight the importance of other genetic factors and/or gene-environment interactions yet to be identified.

The current study is generalizable to women younger than 55 years of age at the time of first breast cancer diagnosis. Whether the results are applicable to older women remains to be evaluated. Strengths of the study include the population-based design, the increased number of CBCs, and the detailed family histories. Because of the large numbers of CBCs, we were able to investigate in fine detail the effect of relatives' ages at breast cancer diagnosis and age in conjunction with a family history of bilateral breast cancer. Nevertheless, the current study also had some shortcomings. Despite the large sample size, some subgroup analyses were still precluded because of small numbers. We incorporated a PRS of 67 known breast cancer risk loci into the analyses but recognize that additional loci have recently been identified.[16,48,49] Other truncating mutations in *CHEK2* and mutations in other genes, such as *CDH1* and *TP53*, may be associated with CBC risk, and we did not exclude them in the current design. Although of interest, these mutations are rare, and the fraction of breast cancer attributable to them is likely low. Family history of breast cancer

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was based on self-report and is likely less accurate for second-degree than for first-degree relatives. Finally, only living breast cancer cases were eligible for the WECARE Study. We used cancer registry data to compare women who were eligible for the WECARE II Study and alive with women who were equally eligible except that they were deceased. (This information was unavailable for the WECARE I Study.) We observed that eligible cases who had died were diagnosed with their first breast cancer at an earlier date, at a younger age, and at a later stage compared with eligible cases who were alive. However, this observation was also true of eligible controls who had died compared with eligible controls who were alive, which suggests that it would be unlikely for this selection to bias relative estimates, such as the RRs reported in the current study. Of note, more knowledge is needed on how survival after CBC is influenced by *BRCA1/2* deleterious mutation carrier status and family history of breast cancer.

In conclusion, family history of breast cancer remains a strong risk factor for CBC, even after excluding carriers of deleterious mutations in *BRCA1*, *BRCA2*, *ATM*, *CHEK2**1100delC, or *PALB2* and after adjusting for 67 common breast cancer risk variants. Family history of breast cancer is relatively easy to assess accurately and even in the absence of genetic testing, can inform the assessment of CBC risk and influence first primary breast cancer treatment decisions, such as prophylactic surgery or systemic therapy. Clinicians are urged to obtain and use detailed family histories from young women diagnosed with breast cancer to guide treatment and future screening decisions.

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Disclosures provided by the authors are available with this article at jco.org.

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